ELECTRONIC FILING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPEAL UNDER 35 U.S.C. §134(a) AND 37 CFR § 41.31(a)
FROM FINAL REJECTION OF CLAIMS IN:

Application of:	Pettis *et al.*	Confirmation No.:	7814
Serial No.:	09/606,909	Art Unit:	3767
Filed:	June 29, 2000	Examiner:	Witczak, Catherine Hayes, Michael J.
For:	INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.:	11219-008-999 (P-4901)

Appeal No.: To Be Assigned

APPELLANT'S BRIEF PURSUANT TO 37 CFR § 41.37

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

TABLE OF CONTENTS

TABLE OF AUTHORITIES

FEDERAL CASES

FEDERAL STATUTES

ADMINISTRATIVE MATERIALS

ELECTRONIC FILING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPEAL UNDER 35 U.S.C. §134(a) AND 37 CFR § 41.31(a)
FROM FINAL REJECTION OF CLAIMS IN:

Application of:	Pettis *et al.*	Confirmation No.:	7814
Serial No.:	09/606,909	Art Unit:	3763
Filed:	June 29, 2000	Examiner:	Witczak, Catherine Hayes, Michael J.
For:	INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.:	11219-008-999 (P-4901)

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

This is an appeal under 35 U.S.C. § 134 and 37 C.F.R. §§ 41.35 and 41.37 from a final rejection of claims 2-4, 10-13, 15, 16, and 29 of the above-captioned application in the office action dated September 23, 2008 ("Final Office Action"). A Notice of Appeal was filed on March 19, 2009.

This Appeal Brief is accompanied by : (1) a Petition for Extension of Time including the appropriate fee for three (3) months from May 19, 2009 up to and including August 19, 2009; and (2) a Brief on Appeal Fee Transmittal Sheet.

Payment of the filing fee for this Appeal Brief, as well as any other fees that may be due are authorized to be charged to Jones Day Deposit Account No. 50-3013 as indicated by the accompanying "Brief On Appeal Fee Transmittal" form.

I. REAL PARTY IN INTEREST

Becton Dickinson and Company is the assignee of this application, and the real party in interest. An assignment transferring the right, title, and interest of inventors Ronald J. Pettis, James A. Down, and Noel G. Harvey in connection with the above-captioned application was recorded in the U.S. Patent and Trademark Office on June 29, 2000 at Reel 010979, Frame 0433.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings known to Appellant or Appellant's legal representative, which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 2-4, 10-13, 15, 16, and 29 are rejected.

Claims 1, 5-9, 14, 25-28, and 30-31 have been canceled without prejudice or disclaimer.

Claims 17-24 and 32-39 are withdrawn.

Claims 2-4, 10-13, 15, 16, and 29 are appealed; and are the subject of this appeal.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter encompasses the administration of insulin to a human subject through a hollow needle that penetrates the dermis of the subject's skin so that the depth and exposed height of the needle *outlet* are contained within the intradermal compartment of the skin, and applying pressure effective to control the rate of delivery, so that systemic distribution of insulin having the claimed pharmacokinetic (PK) profile is achieved; *i.e.*, a higher maximum plasma concentration and a higher bioavailability as compared to subcutaneous delivery of insulin.

The description of the placement of the needle outlet within the intradermal compartment of the skin can be found in the specification at, for example, p. 4, *l.* 29 to p. 5, *l.* 21. The description of the application of pressure to control the rate of delivery can be found in the specification at, for example, p. 5, *l.* 22 to p. 6, *l.* 6 and *ll.* 17-21. The description of the delivery of insulin with the improved pharmacokinetic profile claimed can be found in the specification at, for example, p. 7, *l.* 27 to p. 8, *l.* 21 (Example 2) and in Figure 4; *see also*, p. 6, *ll.* 2-4 and p. 7, *ll.* 21-23, reporting the inventors' finding that the intradermal delivery system of the invention provides higher plasma levels of drug than subcutaneous administration.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection, set forth in the Final Office Action, are presented for review:

(1) Whether claims 2-4, 10-13, 15, 16, and 29 are properly rejected under 35 U.S.C. § 103(a) as obvious over:

(a) U.S. Patent No. 5,848,991 to Gross *et al.* ("Gross I") or U.S. Patent No. 5,807,375 to Gross *et al.* ("Gross II") which, as admitted by the Examiner, lack at least two elements of the appealed claims – *i.e.*, the depth/exposed height of the needle outlet contained within the intradermal compartment, and the specified PK profile;[1]

in view of:

(b) the teachings of the following secondary references that do *not* supply the claim elements missing from the primary Gross I and Gross II references:

(i) *transdermal devices that are designed to penetrate the epidermis – not the dermis:* U.S. Patent No. 6,611,707 to Prausnitz ("Prausnitz");

(ii) *vaccines that are not distributed systemically in the bloodstream, and therefore, do not have PK profiles*: Puri *et al.*, 2000, *Vaccine* 18: 2600-12

[1] Rejections of the claimed subject matter on the grounds of inherent anticipation by Gross I were raised during prosecution and have been resolved. (*See*, April 7, 2005 Office Action, at page 4, and Amendment filed October 7, 2005 accompanied by the Declaration of Dr. Gerald Kasting Under 37 C.F.R.§1.132 ("Kasting Decl.") and the Second Declaration of Dr. Ronald J. Pettis Under 37 C.F.R. §1.132 ("Second Pettis Decl.")), *see also*, Amendment filed June 18, 2007 at pp. 7-8 accompanied by Third Declaration of Dr. Ronald J. Pettis Under 37 C.F.R. §1.132 ("Third Pettis Decl."). In response to this rejection, the Appellant: (a) noted that there was no evidence in the record that practicing Gross I would inherently achieve the claimed invention; (b) presented evidence that practicing Gross I does not inevitably result in the claimed invention (Kasting Decl., Second Pettis Decl., and Third Pettis Decl.) ; and (c) requested evidence to the contrary by way of an Examiner's affidavit pursuant to 37 C.F.R. §1.104(d)(2) (October 7, 2005 Amendment at p. 15). The evidence requested from the PTO was not forthcoming, and the rejections were not repeated thereafter.

("Puri"); U.S. Patent No. 6,056,716 to D'Antonio *et al.* ("D'Antonio"); and U.S. Patent No. 6,007,821 to Srivastava *et al.* ("Srivastava"); and

(iii) *drug delivery techniques yielding PKs that differ from the PK profile claimed* Autret *et al.*, 1991, *Therapie* 46: 5-8 ("Autret"), and The Merck Manual of Diagnosis and Therapy (17^{th} ed.) (1999) ("the Merck Manual").

(2) Whether claims 2-4, 10-13, 15, 16, and 29 are properly rejected on the ground of nonstatutory obviousness-type double patenting over:

(a) claims 8 and 10 of copending Application No. 10/868,482;

(b) claims 1, 2, 7, 8, and 50 of copending Application No. 10/867,908;

(c) claims 1-7, 9, 13, 16, 26, 28-30, 32, 35-41, 46-48, 50, 52-54, 57, 59, and 62-64 of copending Application No. 10/487,485;

(d) claim 25 of copending Application No. 11/004,780;

(e) claim 25 of copending Application No. 11/004,778;

(f) claims 1-3, 8, 10-16 of copending Application No. 10/841,992;

(g) claims 66 and 76 of copending Application No. 10/803,735;

(h) claims 22-26, 29-31, and 33 of copending Application No. 10/650,039;

(i) claim 33 of copending Application No. 10/429,973;

(j) claims 65, 71, 72, 75-77, and 82 of copending Application No. 09/893,746;

(k) claims 31, 32, 36, 37, 39, 49, 67, and 73 of copending Application No. 10/028,988; and

(l) claims 69, 72, 83-86, 88, 90, 100, and 103 of copending Application No. 10/028,989

in view of Gross I or Gross II, and Prausnitz, Autret, Puri, D'Antonio, and Srivastava.

VII. ARGUMENT

A. The Rejection for Obviousness Is Erroneous and Should Be Reversed because:

(1) the Examiner Read the Appellant's Teachings into the Prior Art in an Attempt to Reconstruct the Invention; and

(2) the Proposed Combination of Prior Art Lacks Key Features of the Claims and Does Not Render the Invention Obvious

The rejection of the claims as obvious over Gross I or Gross II, in view of Prausnitz, Puri, D'Antonio, Srivastava, Autret, and The Merck Manual is in error and should be reversed.

The Examiner admits that the primary Gross references are not sufficient to render the claims obvious because they are missing two key features of the claims. Using hindsight gained from the inventors' disclosure, the Examiner attempted to reconstruct the invention, and committed (at least) two errors in rejecting the claims. First, the Examiner read the Appellant's teachings into the prior art (Gross) references – a practice which was rejected by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). Still falling short of the claimed invention, the Examiner then resorted to secondary references to allegedly supply the teachings missing from Gross – but, this only compounded the error. The secondary references relied on by the Examiner do not provide the missing elements/teachings, and therefore do not cure the deficiencies of the primary references. Thus, the rejection of the claims is erroneous and should be reversed.

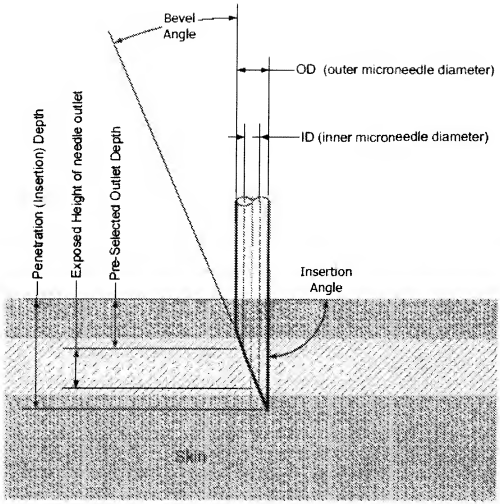
1. The Claimed Invention Requires Positioning the Needle *Outlet* Within the Targeted Intradermal Compartment So That Systemic Distribution of Insulin Having The Specified PK Profile Is Achieved

The claimed subject matter encompasses the administration of insulin to a human subject through a hollow needle that penetrates the dermis of the subject's skin so that the depth and exposed height of the needle *outlet* (of about 0 to 1mm) are contained within the targeted

intradermal compartment and applying pressure to control the rate of delivery, so that systemic distribution of insulin having the claimed pharmacokinetic (PK) profile is achieved.

The method described in the specification limits penetration of the needle to the dermis, reported to be only 1-2 mm thick, *and requires the depth and exposed height of the* ***outlet*** *of the inserted needle to be contained within the targeted intradermal compartment.* The inventors have unexpectedly found that when insulin is administered in this way, it is systemically distributed in the bloodstream with a PK profile that is improved over the traditional subcutaneous route of insulin administration – demonstrating both an improved bioavailability (*i.e.,* increased circulating plasma levels as measured by the **a**rea **u**nder the **c**urve, or "AUC"), and a higher maximum plasma concentration ("C_{max}") as compared to subcutaneous delivery. (*E.g.*, *see* Example 2 and Figure 4 of the Appellant's application).

The inventors recognized that not only depth, but *containment* of the needle *outlet* (*i.e.*, the exposed height of the outlet) within the targeted intradermal compartment significantly affects the resulting pharmacokinetic profile and dose accuracy achieved. Here, the specification describes using microneedles having lengths sufficient to penetrate the dermis and, most importantly, place the *outlet* at depths that contain the exposed height of the needle within the targeted intradermal space. This approach allows for proper sealing of the skin around the needle so as to avoid effusion of drug onto the surface of the skin due to backpressure developed from the force of injection. (Specification at p. 4, *l.* 29 to p. 5, *l.* 21). The diagram below is illustrative:



The use of needles no more than about 2 mm long is recommended. The needle outlet may be formed by a bevel (as shown in the diagram above), located at the tip or on the side of the needle shaft. The needle *outlet* is typically placed at a depth of about 250 μm to 2 mm when the needle is inserted in the skin; preferably, the *outlet* is at a depth of about 750 μm to 1.5 mm, and more preferably at a depth of about 1 mm. (Specification at p. 5, *ll.* 9-14). These parameters, which affect the resulting PK profile and dosing accuracy that are critical for proper insulin delivery, are not taught or suggested by the prior art.

In sum, it was the inventors' recognition that by delivering a substance, such as insulin, within the targeted intradermal compartment via a needle having an outlet height contained

within that compartment, enhanced systemic distribution of the substance is achieved. The claimed delivery parameters are not described or suggested in the prior art. Rather, it was the inventors' unexpected discovery that when insulin is administered in this way – both an improved bioavailability and higher maximum plasma concentration is achieved as compared to the traditional subcutaneous delivery of insulin.

2. The Examiner Admits That The Gross References Are Not Sufficient To Render The Claims Obvious Because They Are Missing Two Elements Of The Claims

The Examiner acknowledges that the primary Gross references lack at least two elements of the appealed claims – (1) the exposed height of the needle outlet claimed (*i.e.*, 0 to 1mm), and (2) the specified PK profile resulting from placement of the needle outlet within the targeted intradermal compartment of skin as claimed. (Office Action, p.3, stating that Gross I and II, "are silent with respect to the needle outlet exposed height of 0-1 mm and the pharmacokinetic profile of the ID delivered drugs).

These claim elements missing from Gross are not supplied by the state-of-the-art knowledge. As evidenced by the prior art of record (discussed *supra*), the dermis was believed to be much thicker than the 1 to 2 mm reported in the instant specification. Therefore, the intradermal target recognized by the inventors is actually much smaller than historically assumed. Thus, the parameters required to ensure penetration and containment of the outlet in the targeted intradermal compartment to achieve the improved PK profile for insulin could not have been derived from the Gross references using the knowledge of one ordinarily skilled in the art.

It is evident that the Examiner concurs that the primary Gross references are not sufficient to render the claimed methods obvious – the rejection under 35 U.S.C. § 103(a) is *not*

based solely on the Gross references, but on their combination with secondary references that allegedly supply the missing features.

3. The Examiner, In Error, Attributes The Appellant's Teachings To Gross To Arrive At A Finding of Obviousness

Gross describes an infusion device to deliver a drug below the epidermis; *i.e.*, to the interface between the epidermis and dermis, or to the interior of the dermis, or subcutaneously. (Gross I: col. 3, *ll.* 38-41; Gross II: col. 5, *ll.* 27-31). To this end, Gross describes a needle that projects outward from the housing preferably by approximately 0.3 to 3 mm, and most preferably 0.3 to 1 mm (Gross I: col. 2, *ll.* 18-21, and col. 4, *ll.* 10-14; Gross II: col. 10, *ll.* 24-27).

Gross is silent as to the configuration of the needle outlet, and does not correlate the depth of the *outlet* to any one of the delivery sites. Gross does not teach the depth or thickness of the layers of skin or boundaries of the intradermal compartment, and Gross does not recognize that the target for intradermal delivery is much smaller than was historically assumed. Gross does not teach that the depth and exposed height of the *outlet* must be contained within the intradermal compartment to achieve the improved PK profile claimed.

In the absence of these recognitions, Gross proposes a range of needle lengths for his device that would not *necessarily* confine the needle *outlet* to the targeted intradermal compartment as required by the claims, and therefore, would fail to achieve the PK profile claimed for insulin. The low end of Gross' range is too shallow for the needle outlet to effectively penetrate the dermis and allow the skin to form a seal around the needle to avoid effusion of drug onto the skin surface; whereas, at the high end of Gross' range, the needle outlet would pass right through the targeted compartment in the dermis.

Despite the lack of any disclosure in Gross concerning the configuration and placement of the outlet, the Examiner contends that the needle lengths disclosed in Gross I and II: "would

put the needle *outlet* at a depth within a range of about 250 μm – 2 mm or 750 μm – 1.5 mm when the housing is set against a patients' skin to achieve ID delivery." (Office Action, p.2, emphasis supplied).

This teaching is found nowhere in Gross I and Gross II. Nor does the Examiner explain how the outlet depths alleged could have been derived from Gross I and II which are totally silent as to the configuration and exposed height of the needle outlet. *Rather, the outlet depths the Examiner attributes to Gross are, apparently, taken directly from the Appellant's specification!* Compare, the Examiner's "calculations" of outlet depths ranging from *250 μm – 2 mm* or *750 μm – 1.5 mm* allegedly derived from the Gross references to the values reported in the Appellant's specification:

> The needle *outlet* is typically at a depth of about *250 μm to 2 mm* when the needle is inserted in the skin, preferably at a depth of about *750 μm to 1.5 mm*, and most preferably at a depth of about 1 mm. The exposed height of the needle outlet and the depth of the outlet within the intradermal space influence the extent of sealing by the skin around the needle. (*Emphasis supplied*).

(Appellant's specification, at p. 5, *ll.* 9-21).

Clearly, the Examiner has run afoul of the Supreme Court's admonition in *KSR* to guard against reading into the prior art the teachings of the invention in issue. *KSR*, 127 S. Ct. at 1742, 82 U.S.P.Q.2d at 1397:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning. *See Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

The Courts have long recognized that a finding of obviousness must be based on knowledge of a person skilled in the art, not on the teachings of the invention in issue. *See*,

Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q. 459 (1966); *In re Dow Chemical*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). Here the Examiner has erroneously used the inventors' own teaching to fill in gaps in the prior art in order to create a facsimile of the claimed invention.

4. The Examiner's Resort To Secondary References In An Attempt To "Fill In" The Teachings Missing From Gross Fails Because The Secondary References Are Equally Deficient

Even after reading the Appellant's teachings regarding the depth of the needle outlet into the Gross references, the Examiner still concluded that without more, Gross I and II were not sufficient to render the claimed invention obvious because the Gross references are missing critical elements of the claimed invention – namely, the exposed height of the needle outlet (from about 0 to 1mm), and the PK profile specified in the claims (a higher C_{max} and bioavailability as compared to subcutaneous delivery of insulin). (Office Action, at p. 3). The Examiner then resorted to secondary references to supply the missing elements. However, this only compounded the error, since the teachings of the secondary references do not supply the claim elements missing from Gross I and II.

(a) Prausnitz Teaches Away From Delivery To The Dermis And Should Not Be Combined With Gross

The Examiner erroneously relies on Prausnitz for the use of microneedles having blunt or flat tips; *i.e.*, an exposed outlet height of 0. However, Prausnitz describes transdermal devices that are designed to penetrate the epidermis – not the dermis – in order to avoid contacting nerves which may cause pain. While microneedles that may have blunt or flat tips are described, Prausnitz recommends that these needles penetrate at a depth of less than 100-150 μm, so as to

only deliver to the epidermis and *avoid penetrating into the dermis* (*see*, Prausnitz at col. 4, *ll.* 7-11) (emphasis added). See the passage below as excerpted from Prausnitz:

> In transdermal applications, the "insertion depth" of the microneedles is preferably less than about 100-150 μm, so that insertion of the microneedles into the skin does not penetrate into the dermis, thereby avoiding contacting nerves which may cause pain. In such applications, the actual length of the microneedles typically is longer, since the portion of the microneedles distal the tip may not be inserted into the skin, the uninserted length depends on the particular device design and configuration. The actual (overall) height or length of microneedles should be equal to the insertion depth plus the uninserted length."

(Prausnitz at col. 4, *ll.* 7-11). Thus, the Examiner's proposed use of a flat-tipped needle in Gross's device with a needle projection of 0.3-3.0 mm (Gross I: col. 4, *ll.* 10-11; Gross II: col. 10, *ll.* 24-25) would contravene Prausnitz's own teaching that the flat-tipped needle not be applied deeper than 0.15 mm (or 150 μm) to avoid penetrating into the dermis and contacting nerves. Since Prausnitz teaches away from delivery to the intradermal compartment it cannot be used to supply the needle configuration missing from the primary Gross references.

By failing to consider the cited references in their entireties, including portions that would lead away from the claimed invention, the Examiner has erroneously found motivation to combine the cited references, where, in fact, none exists. See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); M.P.E.P. § 2141, VI. (Rev. 8, July 2008).

(b) The Vaccine Art Does Not Supply The PK Profile Missing From Gross

As the Examiner admits, Gross I and II are silent with respect to the pharmacokinetic profile achieved for insulin. To fill this gap, the Examiner erroneously relies on the vaccine art (Final Office Action at p. 3 citing Puri, pp. 2609-10; D'Antonio, col. 29, *ll.* 3-23; and Srivastava, col. 19, *l.* 60 – col. 20, l. 25) – but this analysis is flawed in that it suffers from the proverbial

mixing of apples and oranges. Vaccines are not distributed systemically in the bloodstream, and as a result do not display pharmacokinetic profiles. Instead, vaccines are introduced locally, and attract immune cells that "pick up" and process the antigen. These immune cells distribute the processed antigen into the lymphatics which are part of the immune system.[2] This immune response, *not PK profiles*, is precisely what is referred to when Puri describes the increased interaction of antigen with immune cells at p. 2609-10 cited by the Examiner; when D'Antonio refers to the rapid and effective "pick-up" of antigen by the immune system at col. 29, *ll.* 3-23 cited by the Examiner; and when Srivastava describes using heat shock protein ("hsp") as an adjuvant that modulates the immune response at col. 19, *l.* 60 to col. 20, *l.* 25 cited by the Examiner. Tellingly, Srivastava specifically acknowledges that the hsp effect "is mediated through the endogenous, *local, cellular response instead of systemically.*" (Srivastava, col. 6, *ll.* 9-13, emphasis supplied).

Pharmacokinetic studies are meaningless in the vaccine art because practitioners in this field do not gauge the potency of a vaccine by its ability to be circulated in the bloodstream – that is why Puri, D'Antonio and Srivastava do not report PK profiles. Rather, the efficacy of a vaccine is measured by assessing the body's immunological response to the antigen; *e.g.*, the cellular and antibody responses generated against the vaccine antigen that is introduced locally – these are the gauges described in the portions of Puri, D'Antonio and Srivastava cited by the Examiner – not PK profiles of antigen.

[2] The immune cells involved literally ingest the antigen, chew it up, and display pieces of the "processed" antigen on their surface. These cells "present" the processed antigen to other cells in the immune system that orchestrate an immune response. PK profiles play no role in assessing these immunological activities and responses to vaccines. (*See, e.g.*, Puri, "Introduction" at p. 2600 to top left column of p. 2601 and Glenn *et al.*, 1999, Exp. Opin. Invest. Drugs 8: 797-805 (Reference BZ of record) at p. 798, col. 2, last paragraph).

Once again, the Examiner is improperly attributing parameters and properties of the claimed invention into the prior art, and as a result has erroneously read the Appellant's claimed pharmacokinetic profile into Puri, D'Antonio and Srivastava.

(c) Autret Does Not Describe The PK Profile Claimed

Autret is the only reference relied on by the Examiner that describes a drug delivery method and the PK profile achieved by that method[3] – but, *as reported by Autret, the PK profile achieved is not the one required by the claims at issue in this case!* The claims require a PK profile that exhibits *both* a higher maximum plasma concentration (C_{max}) *and a higher bioavailability (AUC) as compared to subcutaneous delivery of insulin.* Autret expressly states, and the data in Autret show (Autret, Fig. 1 and Table 1) that the AUC achieved using Autret's mesotherapy approach is *no different from that obtained by subcutaneous injection.* (Autret at p. 5 of translation, summary). Therefore, Autret does not supply the PK profile required by the claims that is missing from Gross. *See, Ex Parte Affrime*, 2008 WL 460213 at *4 (BPAI Feb. 20, 2008) (reversing Examiner's rejection due to failure to provide evidence that administering the drug according to the prior art teachings would *necessarily* target or achieve the steady state pharmacokinetic profile required by the claims). Again, the Examiner has erroneously read the Appellant's claimed pharmacokinetic profile into the prior art.

The Examiner's contention that Autret describes a higher bioavailability based on a higher C_{max} and T_{max} is not correct. (Office Action pp. 9-10). First, Autret himself uses the AUC as a measure of bioavailability, not C_{max} and T_{max}. (See Autret, Table 1 and p. 5 of the translation, where AUC measurements are used to assess bioavailability, referred to as "BD" in

[3] Autret describes the administration of calcitonin – not insulin as claimed by the Appellant. Nevertheless, since the rejection based on Autret is grounded on obviousness, the Appellant will address Autret's disclosure concerning pharmacokinetic profiles for calcitonin.

the table). Second, bioavailability is customarily assessed by measuring the AUC of a drug's PK profile.

The Appellant has introduced several pieces of evidence to establish the state of the art understanding of PK profiles and how bioavailability is measured, including, *inter alia*, the chapter from the Merck Manual published at the relevant time concerning drug input and distribution (Merck Manual at pp. 2555-2571), a declaration by the inventor (Declaration of Dr. Ronald J. Pettis January 6, 2005 (the "First Pettis Decl.") at ¶¶ 9-14), and a declaration by Dr. Kasting, a professor who is eminently qualified in pharmacokinetics of drug delivery (Declaration of Dr. Gerald Kasting October 6, 2005 (the "Kasting Decl.") at ¶¶ 7-26).

The evidence of record establishes that assessment of bioavailability from plasma concentration-time data involves determining the maximum peak plasma concentration (C_{max}), the time at which the maximum plasma concentration occurs (T_{max}), and the area under the plasma concentration-time curve (AUC) to generate the PK profile for the drug. Of these measurements used to generate the PK profile, it is recognized that bioavailability measurements based on C_{max} or T_{max} can be misleading, and that the AUC is used as the most reliable measure of bioavailability – the AUC "is directly proportional to the total amount of unchanged drug that reaches the systemic circulation" (The Merck Manual, cited by the Examiner, at p. 2560). As one skilled in the art would know, the AUC is essentially viewed as a synonym for bioavailability. The data in the Appellant's application (Example 2) shows improved bioavailability of insulin when using the claimed method, as measured by the AUC shown in Figure 4. (*See also*, First Pettis Decl. at ¶ 9).

The Examiner's use of C_{max} and T_{max} as yardsticks for measuring bioavailability of calcitonin administered in Autret is erroneous – the use of these parameters to assess

bioavailability is disfavored in the art, as they can be misleading. The skilled artisan would routinely look to the AUC as a measurement for bioavailability. In fact, Autret himself uses the AUC – not C_{max} and T_{max} – as a measure of bioavailability.

The Examiner's interpretation is simply at odds with the reference relied on and the understanding of the term in the field of pharmacokinetics. In this respect it is noted that while the Examiner is unquestionably qualified in medical/surgical device technologies, Dr. Kasting's analyses of the facts and conclusions should weigh in heavily on this point since he is eminently qualified in the art of pharmacokinetics of drug delivery. *See, In re Lemin,* 364 F2d 864, 867, 150 U.S.P.Q. 546, 548 (C.C.P.A. 1966) (where the Court reversed the Examiner's rejection noting, "[w]hile the examiner is presumed to be an expert in his field of examination, and while, in the absence of instruction, we might be inclined to agree with him . . . we must, in making determinations under section 103, give weight to the sworn statements of workers skilled in the art as to the meaning to them of symbols with which they, and not we, are familiar. This is particularly so when, as here, questions of convention and custom come into dispute").

Dr. Kasting, eminently qualified in the field of pharmacokinetics, reviewed and analyzed the data in Autret and the Appellant's specification. He came to the conclusion that the PK profile disclosed in Autret is nearly identical to that achieved with subcutaneous injection, and that the improved PK profile claimed by the Appellant is distinct. As explained by Dr. Kasting in his declaration, the PK profile disclosed by Autret is *not* the one claimed by the Appellant. Dr. Kasting confirms that the PK profile disclosed by Autret (*see* Autret, Fig. 1) is virtually identical to the profile for subcutaneous delivery, and does not exhibit both a higher C_{max} and higher AUC, as is required by the pending claims (*see* Kasting Decl. at ¶ 19).

In view of the foregoing, the Examiner's rejection in view of Autret is erroneous and should be reversed.

5. The Claimed Delivery Method Unexpectedly Achieves a PK Profile Superior to Subcutaneous Delivery Of Insulin

Prior to the invention, the term "intradermal delivery" of a drug was used loosely to refer to the delivery of a drug to widely variable depths in the skin (from 1 to 6 mm as described by Hubbard; or 1 to 12.7 mm as described by D'Antonio). Contrary to the prior art understanding, the inventors recognized that, for purposes of intradermal drug delivery, the intradermal target is a discrete compartment having a thickness no greater than 1 to 2 mm beneath the epidermis. In contrast to the prior art, the inventors recognized that for intradermal delivery, the target was much smaller than historically assumed, and that successful delivery required placement of the needle outlet *within* this narrower compartment, so that the substance delivered is deposited *within* the intradermal compartment. This delivery method unexpectedly resulted in improved systemic delivery of the substance as compared to subcutaneous delivery. The claimed methods of drug delivery to the intradermal compartment, and the unexpected results, are neither taught nor suggested by the prior art relied on by the Examiner.

6. The Role of Pressure Has Remained Consistent In Appellant's Remarks

The Appellant's arguments with respect to pressure have been consistent, in contrast to the Examiner's contention (Office Action at p. 10, ¶ 3). Throughout this prosecution, the Appellant has maintained that the requirement of step (a) of claim 29 for inserting the needle, and the requirement of step (b) of claim 29 for pressure are critical for achieving the PK profile of the claims -- however, the absolute value of the applied pressure will vary depending upon the volume and nature of the formulation to be delivered. As explained in the response submitted

January 6, 2005 (at p. 7) and reiterated in the response submitted October 7, 2005, in view of the guidance provided by the specification -- including the working examples -- the absolute value of the pressure used is not critical, in that it can be arrived at for a given formulation by a practitioner exercising ordinary skill. As verified by Dr. Kasting, the experimentation required is not "undue" (*see* Kasting Decl., ¶¶ 13, 14, 15 and 16).

In view of the foregoing, the Examiner's final rejection of claims 2-4, 10-13, 15, 16, and 29 for obviousness under 35 U.S.C. § 103(a), first paragraph, is erroneous and should be reversed.

B. The Rejection of Claims 2-4, 10-13, 15, 16, and 29 on the Ground of Nonstatutory Obviousness-Type Double Patenting Should Be Reversed

The rejection of present claims 2-4, 10-13, 15, 16, and 29 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting over certain claims of copending Application Nos. 10/868,482; 10/867,908; 10/487,485; 11/004,780; 11/004,778; 10/841,992; 10/803,735; 10/650,039; 10/429,973; 09/893,746; 10/028,988; and 10/028,989 in view of Gross I or Gross II, and Prausnitz, Autret, Puri, D'Antonio, and Srivastava is in error and should be reversed.

First, with respect to the rejections over all the copending Applications, for the reasons discussed above, the teachings of Autret, Puri, D'Antonio, Srivastava, Gross I, Gross II, and Prausnitz do not render the claimed invention obvious. Moreover, additional reasons support the separate patentability over certain of the copending applications as set forth in detail below.

The rejection of present claims 2-4, 10-13, 15, 16, and 29 over claims 8 and 10 of copending Application No. 10/868,482 (the "'482 application") is in error. Claims 8 and 10 of the '482 application are no longer pending. Furthermore, the pending claims of the '482 application, *i.e.*, claims 34 and 35, no longer recite a method for administration of a therapeutic

agent into the intradermal compartment to achieve higher a higher tissue bioavailability as compared to other routes of delivery, which was the asserted basis for the rejection. Accordingly, the Appellant submits that the rejection has been rendered moot since there are no longer any conflicting claims in the present application and the '482 application.

The rejection of present claims 2-4, 10-13, 15, 16, and 29 over claims 1, 2, 7, 8, and 50 of copending Application No. 10/867,908 (the "'908 application") is also in error. Claims 1, 2, 7, 8, and 50 of the '908 application are no longer pending. Furthermore, the pending claims of the '908 application, *i.e.*, claims 62-69, no longer recite a method for administration of a biologically active agent into the intradermal compartment to achieve higher a higher tissue bioavailability, faster onset, or increase in amount of deposited agent as compared to delivery to the deeper tissue compartments (*e.g.,* subcutaneous compartment), which was the asserted basis for the rejection. Accordingly, the Appellant submits that the rejection has been rendered moot since there are no longer any conflicting claims in the present application and the '908 application.

The rejection of present claims 2-4, 10-13, 15, 16, and 29 over claim 25 of copending Application No. 11/004,780 (the "'780 application") is also in error. In the present application, in the Office Action dated November 23, 2003 (the "November 2003 Office Action"), the Examiner made a requirement for restriction wherein subject matter directed to methods having a faster onset of detectable plasma levels as compared to subcutaneous injection, were withdrawn from consideration (*see* p. 3 of the November 2003 Office Action). The presently pending claims of the '780 application recite, *inter alia*, that the insulin exhibits a decreased T_{lag} and higher bioavailability as compared to subcutaneous delivery of the insulin. Thus, since the claims of the '780 application are consonant with the restriction requirement set forth in the November 2003 Office Action, the Appellant submits that, pursuant to 35 U.S.C. § 1.121, the

rejection of present claims 2-4, 10-13, 15, 16, and 29 over the claims of the '780 application are prohibited.

The rejection of present claims 2-4, 10-13, 15, 16, and 29 over claim 25 of copending Application No. 11/004,778 (the "'778 application") is also in error. In the November 2003 Office Action, the Examiner made a requirement for restriction wherein subject matter directed to methods having a faster onset of detectable plasma levels as compared to subcutaneous injection, were withdrawn from consideration (see p. 3 of the November 2003 Office Action). The present claims of the '778 application recite, inter alia, that the insulin exhibits a decreased T_{lag} and higher maximum plasma concentration as compared to subcutaneous delivery of the insulin. Thus, since the claims of the '778 application are consonant with the restriction requirement set forth in the November 2003 Office Action, Appellant submits that, pursuant to 35 U.S.C. § 1.121, the rejection of present claims 2-4, 10-13, 15, 16, and 29 over the claims of the '778 application are prohibited.

The rejection of present claims 2-4, 10-13, 15, 16, and 29 over claims 22-26, 29-31, and 33 of copending Application No. 10/650,039 (the "'039 application") is also in error. The '039 application is abandoned, and therefore, since the conflicting claims are no longer present, the asserted basis for the rejection has been rendered moot.

Finally, given that the double patenting rejection is a provisional rejection, Appellant requests that the rejection be held in abeyance until the claimed subject matter is deemed allowable. At that time, the Appellant requests that the rejection be withdrawn and that the instant application be permitted to issue without need of a terminal disclaimer. Given that each of the applications cited in the nonstatutory obviousness-type double patenting rejection are still pending and are filed later in time than the instant application, it is proper once the instant

application is deemed allowable that it be allowed to issue without the need of a terminal disclaimer. *See*, M.P.E.P. §804, I.B.1.

C. Conclusion

For all the reasons set forth above, the rejections of the claims on appeal are in error, and should be reversed.

Respectfully submitted,

by: Jacqueline Benn
Reg No. 43,492

Date: July 31, 2009

Laura A. Coruzzi 30,742

Laura A. Coruzzi (Reg. No.)
JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

VIII. CLAIMS APPENDIX

Currently Pending Claims:

2. (previously presented): The method of Claim 29, wherein the needle is selected from the group consisting of microneedles, catheter needles, and injection needles.

3. (previously presented): The method of Claim 29, wherein a single needle is inserted.

4. (previously presented): The method of Claim 29, wherein multiple needles are inserted.

10. (previously presented): The method of Claim 29, wherein the needle is about 300 μm to 2 mm long.

11. (previously presented): The method of Claim 29, wherein the needle is about 500 μm to 1 mm long.

12. (previously presented): The method of Claim 29, wherein the outlet is at a depth of about 250 μm to 2 mm when the needle is inserted.

13. (previously presented): The method of Claim 29, wherein the outlet is at a depth of about 750 μm to 1.5 mm when the needle is inserted.

15. (previously presented): The method of Claim 29, wherein the outlet has an exposed height of about 0 to 300 μm.

16. (previously presented): The method of Claim 29, wherein the delivery rate or volume is controlled by spacing of multiple needles, needle diameter or number of needles.

17. (withdrawn): A needle for intradermal delivery of a substance into skin comprising means for limiting penetration of the needle into the skin and an outlet positioned such that when the needle is inserted into the skin to a depth determined by the penetration limiting means, leakage of the substance to the surface of the skin is substantially prevented.

18. (withdrawn): The needle of Claim 17 wherein the outlet is at a depth of about 500 μm to 2 mm when the needle is inserted into the skin.

19. (withdrawn): The needle of Claim 18 wherein the outlet is at a depth of about 750 μm to 1.5 mm when the needle is inserted into the skin.

20. (withdrawn): The needle of Claim 17 which is about 300 μm to 2 mm long.

21. (withdrawn): The needle of Claim 20 which is about 500 μm to 1 mm long.

22. (withdrawn): The needle of Claim 17 which is contained in a device comprising a reservoir in fluid communication with the needle.

23. (withdrawn): The needle of Claim 22 which is contained in a device further comprising pressure-generating means for delivering the substance through the needle.

24. (withdrawn): The needle of Claim 23 wherein the pressure-generating means provides variable control of substance delivery rate.

29. (previously presented): A method for administration of insulin to a human subject, comprising delivering the insulin through the lumen of a hollow needle into an intradermal compartment of the human subject's skin, which method comprises

(a) inserting the needle into the subject's skin so that the needle penetrates the intradermal compartment, and the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, wherein the outlet has an exposed height of about 0 to 1 mm; and

(b) delivering the insulin through the lumen of the needle with the application of pressure in an amount effective to control the rate of delivery of the insulin , so that the insulin is delivered through the lumen of the needle into the intradermal compartment and distributed systemically exhibiting a higher maximum plasma concentration and a higher bioavailability as compared to subcutaneous delivery.

32. (withdrawn): The method of claim 29, wherein the drug is used for the treatment of toxicity.

33. (withdrawn): The method of claim 32, wherein the drug is an antitoxin.

34. (withdrawn): The method of claim 29, wherein the drug is used to control pain.

35. (withdrawn): The method of claim 34, wherein the drug is selected from a group consisting of an opioid, an analgesic, or an anesthetic.

36. (withdrawn): The method of claim 29, wherein the drug is used to control thrombosis.

37. (withdrawn): The method of claim 36, wherein the drug is selected from a group consisting of heparin, coumadin, or warfarin.

38. (withdrawn): The method of claim 29, wherein the drug is used to control or eliminate infection.

39. (withdrawn): The method of claim 38, wherein the drug is an antibiotic.

IX. EVIDENCE APPENDIX

1. Autret *et al.* ("Autret") 1991, "Comparison of the plasmatic concentration and the tolerance of a single dose of human calcitonin following intradermal and subcutaneous administration," Therapie 46, 5-8 (with English language translation). This reference was admitted into the record by the examiner on 15 June 2004 (in the Office Action dated 06/15/04).

2. D'Antonio *et al.* ("D'Antonio"), U.S. Patent No. 6,056,716 (2 May 2000). This reference was admitted into the record by the examiner on 7 April 2005 (Reference A on Notice of References Cited ("PTO-892") attached to Office Action dated 04/07/05).

3. Glenn *et al.*, 1999, "Advances in vaccine delivery: transcutaneous immunisation," Exp. Opin. Invest. Drugs 8: 797-805. This reference was entered into the record by the examiner on 24 November 2003 (Reference BZ on Information Disclosure Statement ("IDS") attached to Office Action dated 11/24/03).

4. Gross *et al.* ("Gross I"), U.S. Patent No. 5,848,991 (15 December 1998). This reference was admitted into the record by the examiner on 26 April 2002 (Reference on IDS attached to Office Action dated 04/26/02).

5. Gross *et al.* ("Gross II"), U.S. Patent No. 5,807,375 (15 September 1998). This reference was admitted into the record by the examiner on 4 January 2007 (in the Office Action dated 01/04/07).

6. Hubbard *et al.* ("Hubbard"), U.S. Patent No. 5,505,694 (9 April 1996). This reference was admitted into the record by the examiner on 31 October 2007 (Reference A38 on IDS attached to Office Action dated 10/31/07).

7. The Merck Manual of Diagnosis and Therapy ("the Merck Manual") 1999, 17th Edition, Beers & Berkow, ed., Merck Research Laboratories, Division of Merck & Co., Inc., Whitehouse Station, NJ, pp. 2559 2567. This reference was admitted into the record by the examiner on 24 November 2003 (Reference CK on IDS attached to Office Action dated 11/24/03).

8. Prausnitz *et al.* ("Prausnitz), U.S. Patent No. 6,611,707 (26 August 2003). This reference was admitted into the record by the examiner on 4 January 2007 (in the Office Action dated 01/04/07).

9. Puri *et al.* ("Puri") 2000, "An investigation of the intradermal route as an effective means of immunization for microparticulate vaccine delivery systems," Vaccine 18, 2600-2612. This reference was admitted into the record by the

examiner on 7 April 2005 (Reference U on PTO-892 attached to Office Action dated 04/07/05).

10. Srivastava *et al.* ("Srivastava"), U.S. Patent No. 6,007,821 (28 December 1999). This reference was admitted into the record by the examiner on 23 February 2006 (Reference A on PTO-892 attached to Office Action dated 02/23/06).

11. Declaration of Dr. Gerald B. Kasting under 37 C.F.R. 1.132, 6 October, 2005 ("Kasting Decl."). This declaration was admitted into the record by the examiner on 23 February 2006 (in the Office Action dated 02/23/06).

12. Declaration of Dr. Ronald J. Pettis under 37 C.F.R. 1.132, 6 January 2005 ("First Pettis Decl."). This declaration was admitted into the record by the examiner on 7 April 2005 (in the Office Action dated 04/07/05).

13. Declaration of Dr. Ronald J. Pettis under 37 C.F.R. 1.132, 6 October 2005 ("Second Pettis Decl."). This declaration was admitted into the record by the examiner on 23 February 2006 (in the Office Action dated 02/23/06).

14. Declaration of Dr. Ronald J. Pettis under 37 C.F.R. 1.132, 15 June, 2007 ("Third Pettis Decl."). This declaration was admitted into the record by the examiner on 31 October 2007 (in the Office Action dated 10/31/07).

X. RELATED PROCEEDINGS APPENDIX

None.